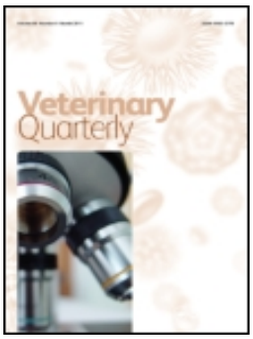

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Clinical efficacy of florfenicol in the treatment of calf respiratory tract infections

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SUMMARY

This paper reports on a study of the aetiology of calf pneumonia and the clinical efficacy of florfenicol, a new antibiotic in Turkey. Twenty-seven weaned and unweaned calves (13 males and 14 females) between 1 and 16 months of age brought to the clinics of Selçuk University, Faculty of Veterinary Science.

Broncho-alveolar lavage (BAL) fluid samples were taken from the animals diagnosed to have upper respiratory tract infection associated with bronchitis (N=2), bronchitis (N=5), bronchopneumonia (N=4), pneumonia (N=3), pleuropneumonia (N=11), bronchopneumonia plus pulmonary oedema (N=2) based on the results of the clinical and laboratory examinations. Then microbiological isolation and antibiotic culturing were performed. The animals were treated with 1 ml/15 kg (20 mg/kg) florfenicol (Nuflor®, DIF) twice within 48 hours via intramuscular injection. At the end of the treatment, 23 of the weaned and unweaned calves were completely healed, 1 calf had died and 3 calves showed no healing. The results of BAL samples and microbiological examinations of the 3 calves that did not respond to the treatment indicated that these cases were affected by mixed infections of yeasts, fungi, and bacteria. Widespread pleuropneumonia was observed. According to the results of the microbiological examination of the BAL samples, *Mannheimia (Pasteurella) haemolytica* had the highest isolation rate (25%) compared with the other isolated bacteria, namely, *Klebsiella pneumonia* (20%), *Actinomyces pyogenes* (15%), *β-hemolytic streptococci.* (10%), *Staphylococcus spp.* (5%), and *E. coli* (5%). The study also revealed fungi [*Penicillum spp.* (5%) and *Aspergillus spp.* (5%)] and two calves (10%) had a yeast infection..

We conclude that florfenicol has a high bacteriological and clinical efficacy (100% and 96% respectively) in the treatment of calf respiratory tract diseases.

INTRODUCTION

Each year, infectious pneumonia, a major problem in stock-breeding, causes large economical losses in our country as in European countries and USA. The rate of losses due to bovine respiratory tract diseases ranges from 37 to 52%. The economic loss caused by this disease in Northern America is estimated between 250 million and 1 billion US Dollars (19, 34). Bacteria, viruses, mycoplasmas, yeasts and parasites play an important role in the aetiology and pathogenesis of infectious pneumonia in calves (2, 4, 6, 8 , 9). It is known that viruses are the primary agent in this disease and among them, respiratory syncytial virus (RSV), parainfluenza-3 virus (PI-3), bovine herpes virus 1 and bovine viral diarrhoea/mucosal disease virus (BVD/MDV) play an important role (8, 9,12,35). *Pasteurella multocida, Mannheimia haemolytica, Haemophilus somnus, Actinomyces pyogenes, Mycoplasma spp.* and *Ureaplasma spp.* are reported to cause secondary bacterial infections (2,3,4,5,12,14,16,21,30,35).

During a study performed in the Konya region , *Mannheimia haemolytica* was reported to have the highest isolation rate (38 %) compared with other isolated bacteria, namely, *Staph. aureus* (8.3%), *Staphylococcus spp.* (8.3%), *Corynebacterium spp.* (8.3%), *Acinetobacter spp.* (8.3%), *K. pneumonia* (8.3%), *Pr. mirabilis* (2.8%), *Pseudomonas spp.* (2.8%), *A. pyogenes* (2.8%) and *Aspergillus spp.* (2.8%) (4).

In Turkey, the broad-spectrum antibiotic chloramphenicol has been widely used for the treatment of calf acute respiratory tract diseases for years. However, the administration of this antibiotic in fattened stocks is forbidden since it can cause bone marrow suppression in humans, depending on the dose, and aplastic anaemia independent of the dose. Florfenicol is a derivative of thiamphenicol. It has been reported that the *in vitro* potency of florfenicol against, pathogenic microorganisms is higher than that of chloramphenicol and thiamphenicol (36), and that its levels in bronchial secretions are higher than the minimum inhibitor concentrations necessary to affect secondary pathogens causing respiratory tract diseases (33). Each millilitre of sterile Nuflor® Injectable Solution contains 300 mg of florfenicol, 250 mg n-methyl-2-pyrrolidone, 150 mg propylene glycol, and polyethylene glycol q.s. Florfenicol is detectable in the serum of most animals up to 60 hours after intramuscular administration of a mean concentration of 0.19 µg/mL. The protein binding of florfenicol is 12.7%, 13.2%, and 18.3% at serum concentrations of 0.5, 3.0, and 16.0 µg/mL, respectively. It is primarily bacteriostatic and acts by binding to the 50S ribosomal subunit and inhibiting bacterial protein synthesis. It should not to be used in cattle of breeding and calves under one mounth age. The effects of florfenicol on bovine reproductive performance, pregnancy, and lactation have not been determined. Intramuscular injection may result a in local tissue reaction that lasts longer than 28 days. This may result in trim loss of edible tissue at slaughter. Florfenicol is very active against *Mannheimia haemolytica* (MIC90 1.0 µg/ml), *P. multocida* and *H. somnus* (MIC90 0.5 µg/ml). Some pharmacokinetic values of second dose florfenicol administered intra muscularly (i.m.) are C_{max} (µg/ml): 4.11(0.72, T_{max} (h): 3.17(1.47, AUC (µg.h/ml): 85.2(10.5 in the serum and C_{max} (µg/ml): 3.22(0.61, T_{max} (h): 7.00(4.82, AUC (µg.h/ml): 75.8(7.25 in the tissue (26). It has been reported that florfenicol treatment, which is not associated with bacterial resi-

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Table 1. Sensitivity criteria and antibiotic content of disks in antibiotic susceptibility tests (22)

		FA	+C	En	E	Fm	T+S	OT	G
Diameter	**Sensitive**	(19	(13	(21	(23	(26	(16	(19	(15
Test Disk	Intermediate	15-18	14-17	16-20	14-22	21-25	11-15	15-18	13-14
(mm)	Resistant	(14	(13	(15	(13	(26	(10	(14	(12
Disk contents	**(mcg)**	30	20+10	5	30	30	1,25+23,75	30	10

F:Florfenicol:Amoxicillin+Clavulanic acid
E:Erythromycin:Flumequine
OT:Oxytetracycline:Gentamicin
En:Enrofloxacin
T+S:Trimethoprim+ sulphamethoxazole

stance, results in a high cure rate compared with 71%, 64%, and 67% of M. haemolytica resistant to oxytetracycline, ampicillin, and penicillin, respectively (27).
The treatment of respiratory tract diseases covers the elimination of predisposing factors, selection of a suitable antibacterial medicine, and supportive treatment. The success of treatment depends largely on a good knowledge of aetiological factors (8). The aim of this study is to evaluate the aetiology of calf pneumonia and the clinical efficacy of florfenicol, a new antibiotic in Turkey.

MATERIALS AND METHODS

The subjects of the study were 27 weaned and unweaned calves (13 males and 14 females) between 30 and 250 kg liveweight and between 1 and 16 months of age brought to the clinics of Selçuk University, Faculty of Veterinary Medicine. The breeds of the calves were as follows: 17 Holstein, 4 Simmental, 3 Montafon, 2 domestic and 1 Charolais. For the comparison of laboratory variables, 10 healthy Holstein unweaned calves were used as the control group.

Clinical examinations
All calves were clinically examined and their general condition, fever, cough, nasal discharge, rate of breathing, type and characteristics of breathing, auscultation and percussion findings were recorded. For laboratory examinations (complete blood count and venous blood gases analyses), anticoagulated blood and broncho-alveolar lavage (BAL) samples were taken from calves clinically diagnosed with respiratory tract infections, based on the results of the clinical examination. BAL samples were cytologically evaluated, and microbiological isolation and antibiotic culturing were applied.

Cytological examinations
BAL samples were taken using a transtracheal method under aseptic conditions. For this purpose, an area covering the top 1/3 of the right side of the neck was shaved and disinfected. The trachea was entered by means of a blood sampling cannula and BAL samples were taken by infusing into and then aspirating from the carina 25 ml of 0.9 % physiological serum with the help of a sterile propylene catheter introduced through the cannula. This process was repeated three times. A part of the aspirated samples was reserved for aerobic bacterial and mycotic isolations. The remaining part was centrifuged at 3000 rpm for 15 minutes after the number of cells was counted. The differential cell count was determined by using Wright's-Giemsa staining methods on the sediment. Cytological smears were evaluated for the existence of epithelial cells, bacteria, fungi, and yeasts.

Microbiological examinations
BAL samples aseptically taken from the calves were inoculated into blood agar base (Oxoid) containing 7 % sheep erythrocytes, MacConkey's Agar (Oxoid) and Sabouraud's Dextrose Agar (Difco) and incubated at 37°C. Microorganisms isolated from the control samples prepared every 24 hours were identified by means of their cultures, morphological, and biochemical characteristics (22, 25).
Isolated bacteria were subjected to antibiotic sensitivity tests with the disk diffusion method (7, 22) in Mueller-Hinton Agar (Difco). Each antibiotic disk (florfenicol 30 µg, erythromycin 15 µg, oxytetracycline 30 µg, amoxicillin 20 µg + clavulanic acid 10 µg, flumequine 30 µg, gentamicin 10 µg, enrofloxacin 5 µg, trimethoprim 1.25 µg + sulphamethoxazole 23.75 µg) was evaluated according to their circular inhibition zones (7, 22). For the florfenicol disk, a (14 mm zone was accepted as resistant, a 15-18 mm zone as intermediate sensitive, and a (19 mm zone as sensitive (Table 1).

Blood analyses
White blood cell count (WBC), red blood cell count (RBC), haematocrit (Hct), haemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), and mean erythrocyte haemoglobin concentration (MCHC) were determined in EDTA-containing blood samples taken for hematological examination (Medonic-Biobak®-CA530). In blood gas analyses, blood pH, pCO_2, pO_2, HCO_3, BE, O_2SAT, O_2CT, Na^+, K^+ and ionized Ca^{++} (ICa) concentrations were measured (288-Ciba Corning®).

Statistical analyses
For data analysis, two sample t test's were used, using (Minitab® for Windows) . The outcome data of the subjects with respiratory tract infection was thus compared to the data for the control group (18).

Treatment procedures
All of the calves were hospitalized throughout the treatment. During the treatment phase, florfenicol in a 300 mg/ml preconstituted injectable solution ((Nuflor®, DIF) was administrated intramuscularly in two doses of 20 mg/kg body weight given 48 hours apart. Clinical examinations were repeated daily. The efficacy of the treatment, prognosis, and complications, such as pain and swelling in infectious areas, were evaluated.

FINDINGS

Clinical findings
High fever (37.7 to 41.1 (C), increased pulse rate from (80 to 200 beats/min) and the respiratory rate of (25 to 107), sero-

Table 2. Haematological and venous blood gas findings in healthy and diseased calves (x±Sx).

		Healthy (n:10)	Diseased (n:27)	p
RBC	10^6/mm³	7.82±0.74	7.57±0.42	0.78-
Hb	g/dl	10.02±1.1	9.18±0.38	0.52-
Hct	%	33.20±3.6	29.20±1.8	0.36-
WBC	10^3/mm³	11.7±3.2	16.9±4.2	0.023*
MCV	um³	33,20±3,6	41.4±2.1	0.64-
MCHC	g/dl	31.5±0.1	32.9±2.2	0.55-
PH		7.402±0.02	7.366±0.01	0.25-
pCO2	MmHg	37,00±3,1	59.50±2.6	0.0002***
pO2	MmHg	30.72±1.5	23.67±1.4	0.0044**
HCO_3^-	mEq/L	29.9±0.6	31.7±1.2	0.032*
BE	mEq/L	3.6±0.5	4.9±2.2	0.045*
O_2SAT	%	54.66±2.6	37.8±3.1	0.0007***
O_2CT	ml/dl	7.06±0.65	5.62±0.48	0.11-
Na^+	mEq/L	132.6±0.39	138.6±0.45	0.58-
K^+	mEq/L	3.864±0.18	3.941±0.09	0.38-
Ca^{++}	mEq/L	1.03±0.15	0.84±0.23	0.65-

*: p<0.05 **: p<0.01 ***: p<0.001

Table 3. Total and differantial cell counts of broncho-alveolar lavage fluid in healthy and diseased calves (x±Sx).

		Healthy (n=10)	Diseased (n=27)	p
Total cell	10^6/ml	320±170	330±130	0.55-
Macrophage	%	66.07±4.5	23.6±3.6	0.0006***
Neutrophil	%	9.17±3.3	45.7±5.9	0.0001***
Lymphocyte	%	13.28±3.2	11.13±2.0	0.35-
Ciliated epithelia	%	3.74±0.87	8.17±1.4	0.020*
Other epithelia	%	7.74±1.6	11.4±2.5	0.25-

*: p<0.05 **: p<0.01 ***: p<0.001

mucous-mucopurulent nasal discharge, cough, sensitivity in the larynx (17) and the trachea (21), and abnormal auscultation and percussion findings were noted in weaned and unweaned calves diagnosed to have upper respiratory tract infection. The animals had respiratory tract infection plus bronchitis (N=2), bronchitis (N=5), bronchopneumonia (N=4), pneumonia (N=3), pleuropneumonia (N=11), bronchopneumonia plus pulmonary oedema (N=2) according to the results of the clinical and laboratory examinations. During auscultation, harsh vesicular sounds, tubular sounds, wet and dry roaring and, in some cases, aphonic areas (N=3) were detected. During percussion, some regional matite and pain were detected in some calves.

Outcome of the intervention

At the end of the treatment, 23 of the calves were completely healed, 1 calf had died, and 3 calves showed no healing. Within the first 24 hours of the injection, the healed calves showed a decrease in fever, nasal discharge and cough, an increased appetite, and an improved general condition. Only three of the healed calves were given an additional dose. As indicated in the anamnesis, these calves had previously been treated, without success, with an other antibiotic and all of them were clinically healed with florfenicol treatment.

Results of BAL fluid samples

The results of BAL fluid samples and microbiological investigation of the 3 calves that did not respond to the treatment revealed that these calves had mixed infections with yeasts, fungi and bacteria. Clinical healing was achieved after these calves were given orally/ 30 mg/kg ketoconazole once a day for 20 days (6). During the autopsy on the only calf that died, adhesions between pleurae and costae, pneumonia areas with small focal abscesses in the cranial lobes, and atypical interstitial pneumonia in diaphragmatic lobes were observed. An egg-sized focal emphysema with a taut capsule extending over the edge of the pleura was observed in the caudal lobe. Interstitial emphysema was noted on the cross-section of this area.

Haematological findings

The results of haematological studies showed that , while a significant ($p<0.05$) increase was detected in the WBC of the calves suffering from respiratory tract infection, venous blood gas analyses indicated a significant ($p<0.05$) increase in pCO_2, HCO_3 and base excess concentrations, and a very significant ($p<0.01$) decrease in pO_2 and O_2SAT concentrations (Table 2).

Cytological findings

Total and differential cell counts were determined by using Wright's-Giemsa stains on the BAL fluid samples (Table 3). In comparison with the control group, the infected calves showed an insignificant ($p>0.05$) increase in total cell count and an insignificant ($p>0.05$) decrease in the lymphocyte count. There was a very significant ($p<0.001$) increase in macrophage and neutrophil counts and a significant ($p<0.05$) increase in the columnar epithelium count. BAL samples from the infected calves which were not given any antibiotics previously exhibited the existence of aerobic bacteria together with yeasts (N=2) and fungus (N=1).

Microbiological findings

Twenty microorganisms from BAL fluid samples were isolated (bacteria =16, fungal =2 and yeast =2). The list of the isolated microorganisms are given in Table 4, along with their percentages.

The list of the bacteria isolated from the BAL fluid samples taken from the calves are given in Table 5, along with the complete results of the antibiotic sensitivity tests.

According to the tests of antibiotic sensitivity, the bacteria isolated from the calves whose BAL fluid samples showed bacterial growth were found to be 100 % sensitive to florfenicol (N=16) and this was followed by amoxicillin plus clavulanic acid (N=13), enrofloxacin (N=11), erythromycin (N=5), flumequine (N=5), trimethoprim plus sulfamethoxazole (N=5), oxytetracycline (N=5), and gentamicin (N=2), respectively. No growth was observed in the tracheal lavage samples taken from 11 calves.

DISCUSSION

In this study, according to the results of the clinical and laboratory examinations, 11 of the 27 BAL fluid samples taken from the weaned and unweaned calves diagnosed to have upper respiratory tract infection plus bronchitis (N=2), bronchitis (N=5), bronchopneumonia (N=4), pneumonia (N=3), pleurapneumonia (N=11), or bronchopneumonia plus pulmonary oedema (N=2) showed no evidence of bacterial growth. Various microorganisms grew in the remaining 16 samples (Table 4, 5). After florfenicol treatment, 23 of the 27 calves healed, completely. 3 calves did not respond to the treatment, and 1 calf (no. 20) died. The yeast and fungus

Table 4. Results of microbiological analyses from broncho-alveolar lavage fluid samples.

Microorganisms	n	%
M. haemolytica	5	25
K. pneumonia	4	20
A. pyogenes	3	15
ß-haemolytic streptococci	2	10
Staphylococcus spp.	1	5
E. coli	1	5
Penicillium spp.	1	5
Aspergillus spp.	1	5
Yeast	2	10
Total	20	100

(Penicillum spp and Aspergillus spp) found in the BAL samples of the calves that did not respond to treatment indicated that these animals suffered from mixed infections. The autopsy findings of calf no. 20 showed advanced pleuropneumonia together with sepsis, widespread pleural adhesions, and ballooning focal emphysemas.

The exchange of gases and the acid-base balance are affected by respiratory tract diseases. Small changes in blood pH (an increase or decrease of 0.05) affect ventilation. In dogs and cats, changes in blood pH quickly activate compensatory mechanisms (17). In this study, pH changes as well as increases in HCO_3 and base excess concentrations in parallel to hypercapnia were detected in the infected calves ($pCO_2 > 45$ mmHg) and are indications of the functioning of compensatory mechanisms. The changes in pO_2 and O_2SAT concentrations observed in the infected calves indicates that the lungs were trying to adjust the blood CO_2 concentration by hyperventilation. The significant ($p<0.05$) increase in WBC concentration in the infected calves in this study is an indication of the constant active inflammation (32).

BAL fluid examination is reported to be useful in the evaluation of pulmonary disorders and to be able to give information about the severity of the inflammation (11,15,24,27). An increase in the neutrophil count and a decrease in the macrophage count of less than 5 % was reported to be an indication of constant acute and chronic active inflammation, and during bronchopneumonia, bronchitis, tracheabronchitis, pulmonary fibrosis, and chronic obstructive pulmonary diseases neutrophils can be detected inBAL fluid (10,11,23,27,28). In this study, BAL fluid cytology showed a very significant ($p<0.001$) increase in the neutrophil count in comparison to that of healthy calves and a very significant ($p<0.001$) decrease in the macrophage count. Total cell counts did not change significantly. These data indicate that there was an active inflammation in the lungs. The non-significant increases observed in columnar and other epithelium cell counts indicated that there was inflammatory damage in the lungs. Bacteria, fungi, and yeasts detected in cytological smears are consistent with the microbiological evaluations and prove that BAL cytology can give direction to microbiological analyses. These results show that evaluations made with the help of BAL cytology are useful to diagnose respiratory tract infections.

Major pathogenic microorganisms causing respiratory tract infections are reported to be bacteria, viruses and mycoplasmas, and the most frequently isolated agent in calf enzootic pneumonia is *Pasteurella spp.* (3,12,20). In their study of 130 calves with pneumonia , Amstel *et al.*(2), reported that *M. haemolytica* and *Ps. aeruginosa* were the aetiological agents in 45% and 25% of the cases, respectively, and *E.coli, Klebsiella spp., Staph. aureus, Serratia spp.* and *Neisseria spp.* in the remaining part. Giles *et al.* (13) isolated *M. haemolytica* and *P. multocida* in 11 and 5 samples from animals with moderate *Shipping fever* pneumonia, respectively. Katoh *et al.* (20) isolated *P. multocida* and *M. haemolytica* in respectively 69 (50%) and 12 (8.7%) of cases, respectively, in a 138-case study.

In this study, according to the microbiological results (Table 4), the most important infectious agent was *M. haemolytica* (25%) in most calves and this was followed by *K. pneumonia* (20%), *A. pyogenes* (15%), *ß-haemolytic streptococci* (10%), *Staphylococcus spp.* (5%), *E. coli* (5%), *Penicillum spp.* (5%), *Aspergillus spp.* (5%), and yeasts (10%). The results of this study and the data obtained in our previous studies show that mycotic factors as well as several bacterial factors should be taken into account in the evaluation of respiratory diseases observed in Konya and its vicinity. In addition, these studies revealed that microbiological examinations are necessary and that the success of treatment depends on the identification of the aetiological factors.

In this study, the complete healing of 23 of the 27 weaned and unweaned calves treated with florfenicol and the florfenicol sensitivity of all microorganisms isolated from BAL fluid samples on which growth was observed led us to conclude that this antibiotic can be effectively used in the treatment of calf respiratory tract diseases. Lockwood et al. (27) reported that the results of trials done at 9 different clinics in Europe and USA showed that florfenicol is more effective

Table 5. Isolated microorganisms from broncho-alveolar lavage fluid samples and antibiotic sensitivity testing

		Number of sensitive isolates							
Microorganisms	**Number**	**F**	**A+C**	**ENR**	**E**	**Fm**	**T+S**	**OT**	**G**
M. haemolytica	5	5	5	5	1	2	1	3	1
K. pneumonia	4	4	3	3	1	2	2	1	-
A. pyogenes	3	3	2	1	1	-	-	-	1
ß-haemolytic streptococci	2	2	1	1	1	-	1	-	-
Staphylococcus spp.	1	1	1	-	-	-	-	-	-
E. coli	1	1	1	1	1	1	1	1	-
Total	**16**	**16**	**13**	**11**	**5**	**5**	**5**	**5**	**2**

F:Florfenicol
E:Erythromycin
OT: Oxytetracycline
A+C: Amoxicillin+Clavulanic acid
Fm: Flumequine
G:Gentamycin
ENR: Enrofloxacin
T:trimethoprim+ sulphamethoxazole

than oxytetracycline and amoxicillin in the treatment of acute bovine respiratory system diseases. Mevius and Hartman (29) also reported that the minimal inhibitory concentration values of florfenicol against *M. haemolytica* strain is lower than that for tetracycline, amoxicilline, trimethoprim+sulpha methaxazole, tilmicosin, neomycin, gentamicin, spectinoycine and flumequine.

We conclude that, in our samples of calves with respiratory tract infection, florfenicol was effective and efficient in treating calf respiratory tract diseases with 100% bacterial efficacy and 96% clinical healing when that bacterial growth was observed.

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